able to (I) find evidence that the key residue-encompassing core region in the AcrB trans-membrane domain is monomer-specifically connected to bulk water by up to 3 periplasmic and 1 cytoplasmic water channels, suggesting three alternative routes of proton transfer; (II) provide evidence that contrary to the available crystal structures the outer membrane efflux duct TolC, while freely accessible from the extracellular medium, is locked only on periplasmic side in a sodium-dependent manner; (III) show that the spontaneous binding of the isolated AcrB docking domain to TolC does not induce an opening of the efflux duct within 1μs simulation time, suggesting that either a longer response time or an additional key is required to unlock the channel; (IV) provide evidence that the currently proposed model of the assembled AcrAB-TolC complex is most likely not correct proposing an alternative model that is consistent with all experimental data currently available including the crystal structure of the membrane fusion protein / inner membrane translocase complex of the homologue copper transporter CusBA.

**3356-Pos Board B217**

**Coarse Graining Protein-Phospholipid Interactions and Diffusion with MsbA Flippase**

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Coarse-grained (CG) modeling has proven effective for simulating lipid bilayer dynamics on scales of biological interest. Simulating the dynamics of flexible membrane proteins within the bilayer, on the other hand, poses a considerable challenge due to the complexity of the folding or conformational landscape. In the present work, the multiscale coarse-graining method is applied to atomistic peptide-lipid 'soup' simulations in order to develop a general set of CG protein-lipid interaction potentials. The reduced model was constructed to be compatible with recent CG models developed for protein-protein folding and lipid-lipid model bilayer interactions. The utility of the CG force field was demonstrated by simulation of the MsbA ABC transporter in a mixed DOPC/DOPE bilayer. An elastic network was parameterized to restrain the MsbA dimer in its open, closed and post-hydrolysis conformations while maintaining domain flexibility. Conformational stability enabled long time dynamics simulation of MsbA freely diffusing in a 25 nm membrane patch. Three-dimensional density analysis revealed that a shell of 'annular lipids' solvate the membrane accessible surface of MsbA and its interior substrate binding chamber. The annular lipid shell is a function of the orientation of grooves formed between transmembrane helices and may influence the alternating access mechanism of substrate entry and translocation.

**3357-Pos Board B218**

**The Transporter Associated with Antigen Processing: Molecular Models to Describe the Transport Cycle**

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The transporter associated with antigen processing (TAP) is a component of the peptide-loading complex that assures the presentation of antigenic peptides to the T-cells on the cell surface. Consequently, infected or transformed cells can be destroyed. TAP translocates the antigenic peptides derived from proteasomal degradation into the endoplasmic reticulum (ER) for loading into the major histocompatibility complex (MHC) class I molecules. As part of the antigen presentation mechanism, TAP is targeted by viruses that try to evade the immune system.

TAP belongs to the ABC transporter family, and is formed by two subunits, TAP1 and TAP2. The ABC core of TAP consists of two transmembrane domains (TMDs), providing the translocation pathway, and two nucleotide binding domains (NBDs), forming two ATP binding sites at their interface. TAP couples the hydrolysis of ATP with the transport of its substrates across the ER membrane. While peptide and ATP binding are uncorrelated events, peptide binding triggers ATP hydrolysis, and thus the conformational changes required for peptide transport. The structural features of this coupling mechanism are still not well understood.

Our goal is to identify residues involved in peptide binding, and residues mechanistically important in driving the conformational changes. We present homology modeling of several conformational states of TAP built using crystal structures of other ABC transporters as templates. We used electrostatic potential calculations to characterize the peptide binding site, and structure-based and sequence-based analyses to recognize residues with a key role in controlling the TMD conformational changes. In the absence of crystal structures, our findings show that homology modeling is a valuable tool to gain structural insights into the mechanism of TAP, and may contribute to understand how the NBD-TMD conformational changes are coupled with the transport of the peptides.

**3358-Pos Board B219**

**Transport Properties of the Human Aquaporin HsAQP5**

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Aquaporins are protein channels located across the cell membrane with the role of conducting water or other small sugar alcohol molecules (aquaglyceroporins). The presence of the human aquaporin 5 (HsAQP5) in cells proximal to air-interacting surfaces (eyes, lacrimal glands, salivary glands, lungs, stomach etc.) suggest its potentially important role in ''wetting'' these surfaces. The high-resolution X-ray structure of the HsAQP5 tetramer (PDB code 3D9S) exhibits two important features: (i) lack of the four fold symmetry, common in most of the aquaporins, and (ii) occlusion of the central pore by a phosphatidylserine lipid tail. In this study we investigate the importance of these two features on the transport properties of the human AQP5 by means of molecular dynamics simulations. We found that the asymmetry in the tetramer leads to a distribution of monomeric channel structures characterized by different free energy landscapes felt by the water molecules passing through the channel. Furthermore, the structures' distribution is influenced both by the presence/absence of the lipid tail in the central pore, and by the lipid composition of the bilayer that solvates the HsAQP5 tetramer.

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**Transport Cycle of Mitochondrial Carriers from Internal Symmetries**

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Mitochondrial carriers (MC) are nuclear-encoded transporters which exchange charged molecules across the inner membrane of mitochondria. The common transport cycle of structurally and functionally similar MCs involves transitions between two major cytoplasmic-open (c-) and matrix-open (m-) states. The only available structure of an MC is that of ADP/ATP carrier (AAC) in c-state. Previous computational and experimental work have characterized the binding site and functional conformational changes of AAC, but fallen short of explaining the full transport cycle. MCs are consisted of three structurally similar repeats each composed of two helices. Based on sequence alignments of individual helices across all MCs, a model for conformational changes resulting in m-state is suggested. The model implies that the helices kink or straighten around certain key residues involving prolines and glycines, so that helices in each repeat exchange conformations among each other. In order to get a detailed realistic view of the transport cycle and to obtain an atomic resolution m-state model of AAC, we combined homology modeling with non-equilibrium driven MD simulations. Initially, we generated crude models of the m-state AAC by modeling each helix in each repeat based on its partner helix. We used the crude m-state models as targets in targeted molecular dynamics (TMD) simulations. Besides, we applied time dependent harmonic restraints on certain collective variables reflecting the conformational change between the c-state and the model m-state. The collective variables include dihedrals of the key prolines and glycines along with rotational orientations of the pieces of helices with respect to the binding site region. Here, we present plausible m-state structures of AAC and transition pathways along with several intermediates identified from the common features of the non-equilibrium simulations requiring the lowest work.

**3360-Pos Board B221**

**Understanding Substrate Unbinding from the Sodium-Galactose Co-Transporter vSGLT based on 16 Microseconds of Molecular Simulation**

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We report the results from 16 microseconds of molecular dynamics (MD) simulations carried out on vSGLT using the Anton supercomputer at the Pittsburgh Supercomputing Center. We observed multiple galactose unbinding events as well as instances in which the energizing sodium ion unbind and then rebind to the putative sodium binding site. Using umbrella sampling we calculated the potential of mean force (pmf) for all galactose unbinding trajectories. We will discuss the allosteric interaction between the ion and substrate and the potential for one to control the release of the other via the inner and outer gates.

**3361-Pos Board B222**

**Insight into the Alternating Access Mechanism of the Sodium Symporter Mhp1 using Path Sampling Simulations**

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Sodium coupled co-transporters of the LeuT superfamily use an alternating access mechanism to move small molecules across the cell membrane. A key step